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DESIGN AND DEVELOPMENT OF CONTROLLED RELEASE LISINOPRIL DIHYDRATE TABLET FORMULATION

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ABSTRACT

Objective: The aim of present study was to design and development of controlled release formulation of Lisinopril Dihydrate by wet granulation, direct compression method. Methods: Twelve formulations were prepared by different excipients such as starch, Mannitol, Calcium phosphate, Iron oxide and Magnesium stearate was used. After fixing the ratio of drug and excipients for control release of drug up to desired time, the release rates were modulated by single excipients; combination of two differentiates controlling material. Results: Formulation (F4) successfully sustained the release of drug up to 12 hours. The release data were fit into different kinetic models (zero-order, first-order, Higuchi's equation and Korsmeyer-Peppas equation). The regression coefficient for zero-order kinetics (0.996) were found to be higher when compared with those of the first-order kinetics (0.821), indicating that drug release from formulation (F4) follows zero-order kinetics. The 'n' value lies between 0.45 to 0.89 (Korsmeyer-Peppas model) demonstrating that the mechanism controlling the drug release was anomalous (non-Fickian) diffusion. Conclusions: All the tablet formulations showed acceptable pharmacotechnical properties and complied with in-house specifications for tested parameters. Stability studies were performed as per ICH guidelines and results indicated that the selected formulation was stable. Optimized formulation was tested for their compatibility with Lisinopril Dihydrate by FT-IR studies, which revealed that there is no chemical interaction occurred with polymer and other excipients. Therefore, the results of the kinetic study obtained permit us to conclude that orally controlled Lisinopril Dihydrate matrix tablets, in this case, delivers the drug through a complex mixture of diffusion, swelling and erosion. The drug release profile of the best formulation was well controlled and uniform throughout the dissolution studies.

Keywords: Controlled drug delivery systems (CDDS); Lisinopril Dihydrate; Guar gum; Karaya gum; Xanthan gum.

INTRODUCTION

Lisinopril Dihydrate is a non-sulphydryl category, a drug belonging to the Angiotensin Converting Enzyme inhibitor (sometimes written as ACE inhibitors), a class of drug used primarily in hypertension and some types of chronic heart failure [1-3]. Angiotensin converting enzyme inhibitors were first introduced for the treatment of hypertension in the early 1980's. Captopril was the first drug to be developed [4,5]. Concerns about the potential toxic effects of the sulphydryl group in captopril and the fact that it needed to be given twice or three times a day, led to the development of Lisinopril, a non-sulphydryl derivative [6-8]. So, lisinopril was developed partly to overcome these limitations of captropril. The sulfhydryl-moiety was replaced by a carboxylate-moiety, but additional modifications were required in its structure-based design to achieve a similar potency to captopril [9-12].

The development of sustained / controlled release formulations of Lisinopril Dihydrate is therefore of therapeutic relevance and can be used to provide a consistent dosage through sustaining an appropriate level of drug over time. The simplest and least expensive way to control the release of the drug is to disperse it within an inert polymeric matrix and hydrophilic matrices are an interesting option when formulating an oral sustained release (SR) of a drug [13-16].

The dosage release properties of matrix devices may be dependent upon the solubility of the drug in the polymer matrix or, in case of porous matrices, the solubility in the sink solution within the particle's pore network [17-18].

So, the objective of the present study was to formulate Lisinopril Dihydrate SR matrix tablets using forming agent and excipients such as lactose, magnesium

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stearate and talc were used and to elucidate the release kinetics of Lisinopril Dihydrate from matrices. We attempted a systematic approach to develop twice-daily sustained release Lisinopril Dihydrate matrix tablets.

MATERIAL AND METHODS

Chemicals

Lisinopril dehydrate (Embiotic Laboratories Pvt. Ltd., Banglore), Dicalcium phosphate dehydrate, Pearlitol 25C, Pearlitol 300DC, MCC (112), MCC (101) Maize Starch, PVP-K-30, Pregelatinized Starch, Red Iron Oxide, Yellow Iron Oxide, Magnesium Stearate, Talc were purchased from S. D. Fine Chem. Ltd., Mumbai.

Instruments

Tablet compression machine (Cadmach), Rapid Mixer Granulator (Kevin), Planetary Mixer (PLM) (Kenwood), Disintegration tester (Electrolab (ED-2AL)), Dissolution apparatus (Electrolab (TDT-08L)), Rapid Dryer (Retsch (TG-100)), Particle size analyzer (Electrolab (EMS-8)), LOD (Loss on drying) tester (Mettler Toledo (HB 43)), Hardness tester (Dr. Schleuniger (5Y)), Density tester (Electrolab (ETD-1020)), Blender (Pretime – D), Roche Friabilator USP (Electrolab (EF-1W)), Verniear caliper (Mitutoyo (absolute digimatic)), Digital pH meter (Labindia), HPLC apparatus (Dionex (P-680), Waters (2695), Agilnet (1100), UV-Visible spectrophotometer (Jasco V 530 & Perkin Elmer (Lambda25)), Karl Fischer apparatus (Mettler Toledo (DL 31), Digital weighing balance (Mettler Toledo (AB 204-S)),

Preparation of matrix tablet

Calculate & Weigh Lisinopril dihydrate based on its potency. Dispense all other ingredients as per batch formula and sift Lisinopril dihydrate, DCP dihydrate, Pearlitol 25^0 C through 40 mesh and starch through 200 mesh & colour through 200 mesh. Mixed above ingredients in RMG for 15 minute at slow speed. Sift starch for paste through 100# and prepare the 10% paste as binder. Granulate for 10 mins in RMG at slow speed (75 RPM) along with chopper on, with racking after 5 mins. Dry the wet mass at 60°c till the LOD reaches less than 4.0 %w/w. Rasp the dried granule through 30# Sift dried starch through 100# and magnesium stearate through 60# Mix the rasped granule and sifted dried starch in blender for 20 mins. Add sifted magnesium stearate for 5 mins in the same blender. Compressed the above blend obtained in with their respective punch.

Evaluation of tablets: -

The prepared matrix tablets were evaluated for thickness and diameter, hardness, friability, weight variation, swelling index and uniformity of drug content. The thickness and diameter was measured using vernier callipers (Mitutoyo Corporation, Japan) in mm. The Monsanto hardness tester was used to determine the tablet hardness. Friability of the tablets was determined in a Roche friabilator. Weight variation test was performed according to official method. Drug content for lisinopril dehydrate was carried out by measuring the absorbance of samples at 207.10 nm using Labindia-25 UV/Vis spectrophotometer and comparing the content from a calibration curve prepared with standard lisinopril maleate in the same medium.

In-vitro release study:

In-vitro drug release studies from the prepared matrix tablets were carried out using USP dissolution apparatus type II (Electrolab, Mumbai, India) at 50 rpm. The dissolution medium consisted of 900 ml of 0.1 N HCl and pH 6.8 phosphate buffer, maintained at 37 $\pm$ 0.5°C. The release rates from matrix tablets were conducted in HCl solution (pH 1.2) for 2 h and changed to phosphate buffer (pH 6.8) for further time periods. The samples were withdrawn at desired time periods from dissolution media and the same were replaced with fresh dissolution media of respective pH. The drug release at different time intervals was measured using an ultraviolet visible spectrophotometer (Labindia, Mumbai, India) at 207.10 nm. The study was performed in triplicate. The actual content in samples was read from a calibration curve prepared with standard lisinopril dehydrate.

Kinetic Analysis of dissolution data: -

In order to describe the Lisinopril Dihydrate release kinetics from individual tablet formulations, the corresponding dissolution data were fitted in various kinetics dissolution models: zero order, first order, Higuchi, Korsmeyer Peppas and Hixon Crowell. The results of *in vitro* release profile obtained for all the formulations were plotted in modes of data treatment as follows:-

1. Zero order kinetic model: Cumulative % drug released versus time and formula are as: -

$\mathbf{A_t = A_0 - K_{0t}}$ where At = Drug release at time't', A_0 = Initial drug concentration, K_{0t} = Zero order rate constant (hr^{-1}).

2. First order kinetic model: Log cumulative percentage drug remaining versus time and formula are as follows: -

$\mathbf{Log\ C = log\ C_0 - K_t / 2.303}$ Where, C = Amount of drug remained at time't' C0 = Initial amount of drug. K= First – order rate constant (hr^{-1}).

3. Higuchi's model: Cumulative percentage drug released versus square root of time and formula are as follows.

$\mathbf{C = [D\ (2_{qt} - C_s) C_{st}]^{1/2}}$

Where,

C=Total amount of drug release per unit area of matrix per unit area of matrix [mg/cm^2]

D = Diffusion coefficient of the drug in the matrix

qt = total amount of drug in a unit volume of matrix [mg/cm^3]

A= Total amount of drug in unit volume of matrix

Cs = the solubility of the drug in the matrix porosity of the matrix

t = Time (hrs) at which 'q' amount of drug is released

4. Korsmeyer equation / Peppa's model: Log cumulative percentage drug released versus log time: to study the

mechanism of drug release from the controlled release matrix tablets of lisinopril dehydrate, the release data were also fitted to the well-known exponential equation (Korsmeyer equation / Peppa's law equation), which is often used to describe the drug release behavior from polymeric systems. The formula are as follows: -

$Mt / Ma = Kt^n$

Where, Mt / Ma = the fraction of drug released at time't'. K = Constant incorporating the structural and geometrical characteristics of the drug /polymer system. N = Diffusion exponent related to the mechanism of the release. Above equation can be simplified by applying log on both sides, and we get:

Log Mt / Ma = Log K + n Log t

When the data is plotted as log of drug released versus log time, yields a straight line with a slope equal to 'n' and the 'K' can be obtained from y – intercept.

Fourier Transform Infra-Red Study: FT-IR spectra of the selected formulation were taken and compared with the spectrum of pure drug. The characteristic peaks of drug were checked in the formulation spectra.

Stability Studies: Stability studies of pharmaceutical products were done as per ICH guidelines. These studies are designed to increase the rate of chemical or physical degradation of the drug substance or product by using exaggerated storage conditions.

Method: Selected formulations were stored at different storage conditions at elevated temperatures such as 25°C± 20C / 60% ± 5% RH, 300°C ± 20°C / 65% ±5% RH and 40°C ± 2°C/ 75% ± 5%RH for 90 days. The samples were withdrawn at intervals of fifteen days and checked for physical changes, hardness, friability, drug content and percentage drug release.

Table 1. Tablet composition of different formulations of Lisinopril dihydrate controlled release matrix tablets (F-1 to F-4).

Sr. No.	Ingredients	Formulation No.			
		1	2	3	4
Method of Formulation→		Direct compression	Direct compression	Slugging method	Wet granulation
1	Lisinopril	21.88	21.88	21.88	21.88
2	DCPD	70.12	69.12	99.12	94.12
3	Pearlitol 300DC		70	40	
4	Pearlitol 25C				40
5	MCC (112)	115	45	45	
6	MCC (101)				20
7	Red iron oxide	1	1	1	1
8	Purified Water	QS	QS	QS	QS
9	Magnesium Stearate	2	2	2	2
10	Talc		1	1	
Tablet weight (mg)		210	210	210	210
Remark		Flow problem, Wt. variation	Capping was observed.	Problem in assay, Content uniformity	Drug Release was less

Table 2. Tablet composition of different formulations of Lisinopril dihydrate controlled release matrix tablets (5 to 8).

Sr. No.	Ingredients	Formulation No.			
		5	6	7	8
Method of Formulation		Wet Granulation	Wet Granulation	Wet Granulation	Wet Granulation
1	Lisinopril Dihydrate	21.88	21.88	21.88	21.88
2	DCPD	100.12	100.12	99.12	109.12
3	Pearlitol 25C	40	40	40	40
4	MCC (101)	10			
5	Maize Starch	20	30	10	20
6	Maize Starch (Paste)	5	5	5	5
7	Red Iron Oxide	1	1	1	1
8	Purified Water	QS	QS	QS	QS
9	Dried Maize Starch	10	10	30	10
10	Magnesium Stearate	2	2	3	3
Tablet weight (mg)		210	210	210	210
Remark		Drug Release Was Less	Slight Sticking	Initial Very Fast Release	Drug Release Was Less

Table 3. Tablet composition of different formulations of Lisinopril dihydrate controlled release matrix tablets (9 to 12).

Sr. No.	Ingredients	Formulation No.			
		9	10	11	12
Method of Formulation		Wet Granulation	Wet Granulation	Wet Granulation	Wet Granulation
1	Lisinopril Dihydrate	21.88	21.88	21.88	21.88
2	DCPD	113.12	92.12	91.62	92.62
3	Pearlitol 25C	36	36	36	36
4	Maize Starch	20	35	36.5	36.5
5	Maize Starch (Paste)	5	5	4	4
6	Red Iron Oxide	1	0.5	0.5	0.5
7	Yellow Iron Oxide	---	1.5	1.5	1.5
8	Purified Water	QS	QS	QS	QS
9	Dried Maize Starch	10	15	15	14
10	Magnesium Stearate	3	3	3	3
Tablet weight (mg)		210	210	210	210
Remark		Drug Release Was Less	Not Match With DPDM	Not Match With DPDM	Match With DPDM

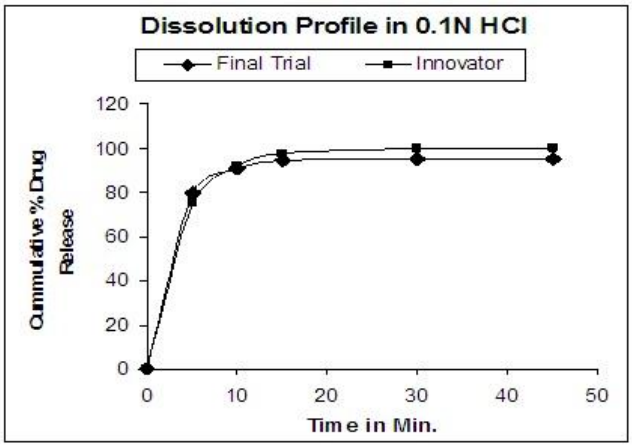
* indicates NIL.

Tablet 4. Granules properties of formulations no. 1 to 12 of Lisinopril Dehydrate controlled release matrix tablets.

Formulation No.	Loss on drying (%w/w)		Bulk density (gm/ml)	Tap density (gm/ml)	Carr's index (%)	Hauser's ratio
	Dried Granules	Final blend				
1	4.56	4.65	0.375	0.6	37.5	1.6
2	3.81	3.61	0.5	0.645	22.481	1.29
3	3.72	3.55	0.487	0.591	17.597	1.214
4	4.02	3.73	0.502	0.601	16.473	1.197
5	3.88	3.58	0.483	0.591	18.274	1.224
6	3.91	3.68	0.483	0.6	19.500	1.242
7	3.5	3.37	0.488	0.597	18.258	1.223
8	3.85	3.66	0.473	0.582	18.729	1.230
9	4.18	4.11	0.487	0.593	17.875	1.218
10	3.99	3.87	0.473	0.587	19.421	1.241
11	3.98	3.78	0.493	0.595	17.143	1.207
12	4	3.76	0.501	0.657	23.744	1.311

Table 5. Tablet properties of formulations formulation no. 1 to 18 Lisinopril Controlled release matrix tablets.

Formulation No.	Average wt.(mg)	Thickness (mm)	Hardness (N)	Disintegration time(min.)	Friability (% w/w)	Assay (%)
1	205-230	3.42-3.52	40-50	Not Applicable		
2	Not Applicable					
3	208-226	3.40-3.48	40-50	2.0-3.0	0.11	91
4	208-215	3.40-3.48	40-50	3.0-3.20	0.15	90
5	208-215	3.40-3.46	45-55	3.0-3.30	0.11	98.93
6	208-213	3.41-3.46	45-55	2.0 -2.10	0.15	99.24
7	208-213	3.41-3.46	45-55	1.45-1.50	0.16	NA
8	208-213	3.41-3.46	45-55	45-50sec	0.21	99.43
9	208-213	3.41-3.47	45-55	2	0.12	101.2
10	208-213	3.41-3.47	50-60	2.10-2.15	0.1	100.5
11	208-213	3.40-3.45	65-70	2.20-2.30	0.08	100.1
12	208-213	3.41-3.45	65-70	2.25-2.30	0.08	100.7



RESULT AND DISCUSSION:

The present investigation was carried out to develop immediate release tablet dosage form of class III drug, Lisinopril Dihydrate. The tablets were prepared by using different excipients. The study was carried out at different conditions of temperature and humidity like 40°C/75% RH, 2-8°C, room temperature & found their physical appearance, impurity level and water content after 2 week, 4 weeks and compare with initial value. The result shows impurity level with some drug and excipient combination increases and also slight changes in appearance but except propyl paraben all were compatible with Lisinopril. Excipients were considered compatible only if the total impurities do not exceed twice times the impurities of initial. The evaluation of formulation parameters reveals Loss on Drying of dried granules and final blend, bulk density, tapped density, Carr's Index, Houser's Ratio and sieve analysis in pre-compression parameters and average weight, thickness, hardness, disintegration time and friability in post compression parameters. LOD as calculated, theoretical moisture content of drug and excipient which was 3.86% w/w, 80 LOD of dried granules maintained in that level NMT ± 1% variation by drying at 60°C and optimize drying time for achieve LOD in particular limit. Initially some flow problem arises in direct compression method powder blend shows poor flow which causes weight variation, problem in content uniformity; but wet granulation method shows good flow properties of granules and final blend. Post compression parameters included weight variation observed, but in final batch tablet ranging 208-213 mg (Target wt-210mg/Tablet) for 20 mg and 103-106 mg (Target wt-105 mg/Tablet) for 2.5 mg tablet formulation, which is less than 5% indicates that the variation in the weight of the tablets is within standard official limits. Thickness of tablets was observed by Vernier Caliper. Thickness of Tablet does not show any measurable deviation in both strengths. Hardness of the tablet was measured in 'Newton' unit in digital harness tester. The hardness of tablets found to be uniform within range 65 N to 70 N for 20 mg and 38-40 for 2.5 mg indicates that the prepared tablets are mechanically stable. Disintegration test was carried out in Electro lab (ED-2AL). Disintegration time for 6 tablets found to be 2.25- 2.30 min for 20 mg and 60-75 sec for 2.5 mg was less than 15 min indicating that disintegration time within the specification limit. The friability was carried out by using Roche Friabilator. The percentage friability of tablet was ranging 0.08% - 0.21% for 20 mg and 0.04-0.08% for 2.5 mg. They are less than the standard limit of 1% indicates that the prepared tablets are mechanically stable.

In the initial formulation drug content uniformity found outside limit but, after that each formulation drug contents ranging from 98%-101.2% which is within the range of 92.5-105% for Lisinopril. It indicates uniform distribution of drug in the tablets of each formulation. *In Vitro* drug release studies revealed were subjected to *in vitro* drug release studies in 0.1 N HCl for 45 min. The drug release studies carried out in dissolution test apparatus using 900 ml of dissolution medium, maintained at 31°C ± 0.5°C. Among all batches dissolution profile of 3 batchs *i.e.* Trail - 10, Batch - 11, Batch - 12 matches with innovator in 0.1N HCl medium. Then they were subjected to match in other two medium i.e. pH 4.5 acetate buffer and match in D.M. Water, but Batch – 10 and Batch - 11 failed to match in D.M. Water medium with innovator. Only Batch 12 matches with a three media with innovator. Thus, Batch-12 was finalized.

CONCLUSION

In this study controlled release matrix tablet of lisinopril dehydrate was prepared by wet granulation technique using guar gum, karaya gum and xanthan gum polymers as retardant. It was found that increase in the concentration in polymeric ratio decreases the drug release. All the tablet formulations showed acceptable pharmacotechnical properties like hardness, friability, thickness, weight variation, drug content uniformity etc. and complied with in-house specifications for tested parameters. Tablet matrices containing 25% guar gum gave better drug release rate over a period of 12 hours. Thus, formulation F-4 was found to be the most promising formulation on the basis of acceptable tablet properties and *in-vitro* drug release. The

kinetic treatment of selected optimized formulation F-4 shows that the regression coefficient for zero-order kinetics were found to be higher when compared with those of the first-order kinetics, indicating that drug release from all the formulations followed zero-order kinetics and the 'n' value lies between 0.45 to 0.89 (Korsmeyer-Peppas model) demonstrating that the mechanism controlling the drug release was Anomalous (non-Fickian) diffusion. Therefore, the results of the kinetic study obtained permit us to conclude that orally controlled lisinopril dehydrate matrix tablets, in this case, delivers the drug through a complex mixture of diffusion, swelling and erosion. Stability studies were conducted for the optimized formulations as per ICH guidelines for a period of 90 days which revealed the stability of the formulations. The results suggest that the developed controlled-release tablets of lisinopril dehydrate could perform better than conventional dosage forms, leading to improve efficacy and better patient compliance. So, the results of demonstrated that guar gum could be successful hydrophilic polymer for the formulation of controlled release matrix tablets of lisinopril dehydrate. *In vitro* dissolution studies indicated a controlled release pattern throughout the 12 hours study period, which was compatible with theoretical release profile. This can be expected to reduce the frequency of administration and decrease the dose-dependent side effects associated with repeated administration of conventional lisinopril dehydrate tablets.

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